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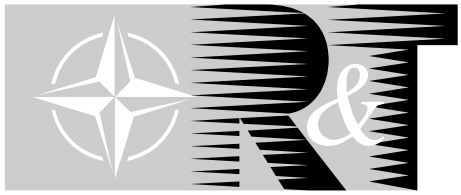

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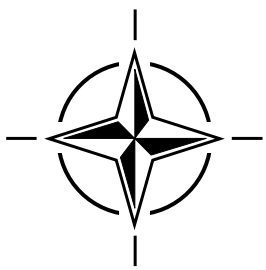
Operational Medical Issues in Hypo- and Hyperbaric Conditions

(les Questions médicales à caractère opérationnel liées aux conditions hypobares ou hyperbares)

Papers presented at the RTO Human Factors and Medicine Panel (HFM) Symposium held in Toronto, Canada, 16-19 October 2000.



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The Research and Technology Organization (RTO) of NATO

RTO is the single focus in NATO for Defence Research and Technology activities. Its mission is to conduct and promote cooperative research and information exchange. The objective is to support the development and effective use of national defence research and technology and to meet the military needs of the Alliance, to maintain a technological lead, and to provide advice to NATO and national decision makers. The RTO performs its mission with the support of an extensive network of national experts. It also ensures effective coordination with other NATO bodies involved in R&T activities.

RTO reports both to the Military Committee of NATO and to the Conference of National Armament Directors. It comprises a Research and Technology Board (RTB) as the highest level of national representation and the Research and Technology Agency (RTA), a dedicated staff with its headquarters in Neuilly, near Paris, France. In order to facilitate contacts with the military users and other NATO activities, a small part of the RTA staff is located in NATO Headquarters in Brussels. The Brussels staff also coordinates RTO's cooperation with nations in Middle and Eastern Europe, to which RTO attaches particular importance especially as working together in the field of research is one of the more promising areas of initial cooperation.

The total spectrum of R&T activities is covered by the following 7 bodies:

- AVT Applied Vehicle Technology Panel
- HFM Human Factors and Medicine Panel
- IST Information Systems Technology Panel
- NMSG NATO Modelling and Simulation Group
- SAS Studies, Analysis and Simulation Panel
- SCI Systems Concepts and Integration Panel
- SET Sensors and Electronics Technology Panel

These bodies are made up of national representatives as well as generally recognised 'world class' scientists. They also provide a communication link to military users and other NATO bodies. RTO's scientific and technological work is carried out by Technical Teams, created for specific activities and with a specific duration. Such Technical Teams can organise workshops, symposia, field trials, lecture series and training courses. An important function of these Technical Teams is to ensure the continuity of the expert networks.

RTO builds upon earlier cooperation in defence research and technology as set-up under the Advisory Group for Aerospace Research and Development (AGARD) and the Defence Research Group (DRG). AGARD and the DRG share common roots in that they were both established at the initiative of Dr Theodore von Kármán, a leading aerospace scientist, who early on recognised the importance of scientific support for the Allied Armed Forces. RTO is capitalising on these common roots in order to provide the Alliance and the NATO nations with a strong scientific and technological basis that will guarantee a solid base for the future.

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Decompression Sickness Research: New Directions

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Summary: DECOMPRESSION SICKNESS RISK REDUCTION was sought throughout the twentieth century by adjusting dive duration and depth combinations. These adjustments hypothetically minimized inert gas supersaturation in tissues during decompression. The newest efforts in decompression sickness research by scientists at the U.S. Naval Medical Research Center in Silver Spring, Maryland, are focused on fundamentally different approaches. We are seeking means of reducing decompression sickness risk by actively eliminating a critical portion of the body's inert gas load; by increasing the volume of inert gas held in solution by the blood; or by blocking the body's response to intravascular bubbles.

Biochemical Decompression

The role of nitrogen in diving and decompression sickness is familiar to all. Fewer people are familiar with the potential for using hydrogen in ultradeep diving, and how this gas may affect decompression sickness risk. Biochemical decompression is the name that we have created for our most radical new approach to reducing decompression sickness risk. Hypothetically, biochemical decompression can be performed using either hydrogen or nitrogen as the diluent for oxygen in a hyperbaric breathing mixture. Both hydrogen and nitrogen have the properties of being inert to mammalian metabolism, but substrates for metabolism by numerous microbial species. If divers were provided with the biochemical machinery to metabolize even a small amount of the hydrogen or nitrogen dissolved in their tissues, significant reduction in decompression sickness risk could be achieved.

Again speaking hypothetically, one might imagine that this biochemical machinery could be offered to the diver in a variety of forms, such as a subdermal or peritoneal implant, a dialysis-type device connected to the blood circulation, or a pulmonary spray. However, even a brief consideration of these approaches makes it apparent that most body locations are unsuited for this purpose. Most locations within the body are approachable only by invasive means, and we certainly would not want the biochemical decompression to be a higher risk procedure than the treatment of decompression sickness itself. Furthermore, most body locations would not accept the implantation of microbial material, due to the response of the immune system.

We have nevertheless succeeded in finding a body location and an approach that have been successful for hydrogen biochemical decompression in both a small and a large animal model (Kayar et al., *Am. J. Physiol., 275*:R677-R682, 1998; Kayar et al., unpublished observations). The large intestine is ideal for our purposes. There are numerous species of microbes that metabolize hydrogen and are part of the normal flora of the large intestines of humans and other mammals, thus eliminating the concerns about an immune reaction. There is a rich blood supply to the intestine, assuring the microbes of good access to hydrogen. The microbes can be delivered to the intestine by mouth, and the end products of their metabolism can be readily lost from the intestines along with other waste products.

The microbial species we selected, *Methanobrevibacter smithii*, has been well studied and is known to be non-pathogenic in humans (Miller and Wolin, *Appl. Microbiol. 131*:12-18, 1982). Its metabolic pathway is:

$$4H_2 + CO_2 \rightarrow 2H_20 + CH_4$$

in which four molecules of hydrogen are converted to two molecules of an innocuous, non-gaseous end product (water). The electron acceptor, CO_2, is abundant in tissues. The secondary end product, methane, is already produced in the intestines of most animals, and escapes harmlessly with other intestinal gases.

Our approach was to surgically inject live cultures of *M. smithii* into the proximal end of the large intestines of rats and pigs. The animals were then placed in a dry hyperbaric chamber that was specially designed for compression with mixtures of hydrogen and oxygen. As the animals breathed hydrogen, some of this gas was metabolized by the microbes in the intestines. Chamber gases were monitored by gas chromatography. The rate at which the animals released methane was measured as a simple and non-invasive method of following the rate of hydrogen removal by the microbes (Figure 1). Animals that received these microbial treatments had a significantly lower incidence of decompression sickness compared to untreated animals, and also compared to surgical control animals that received intestinal injections of saline (Figures 2 and 3). For both rats (Figure 2) and pigs (figure 3), decompression sickness incidence was cut approximately in half by the microbial treatments. Mathematical analysis suggests that this decreased risk of decompression sickness was achieved by eliminating only roughly 5% percent of the total body burden of hydrogen in these animals.

Paper presented at the RTO HFM Symposium on "Operational Medical Issues in Hypo- and Hyperbaric Conditions", held in Toronto, Canada, 16-19 October 2000, and published in RTO MP-062.

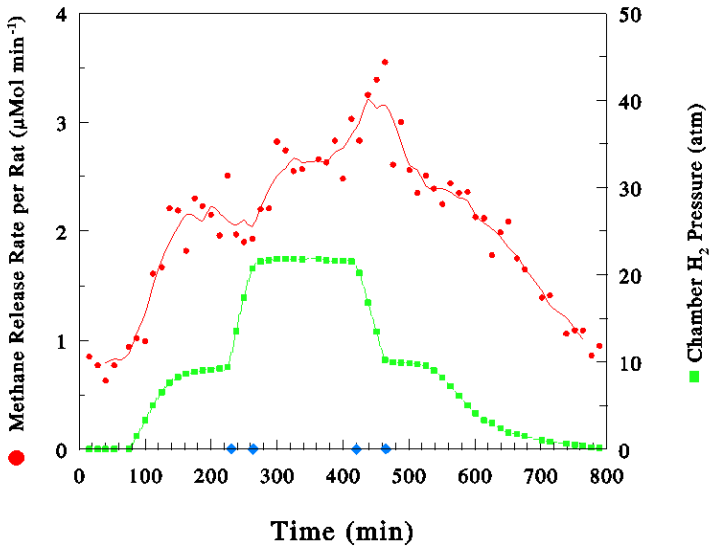

Figure 1. As rats treated with hydrogen-metabolizing microbes breathed hydrogen at increasing pressures, the amount of methane they released increased. As hydrogen was removed from the chamber, methane release rate from the rats increased briefly (probably reflecting supersaturation with hydrogen), and then decreased.

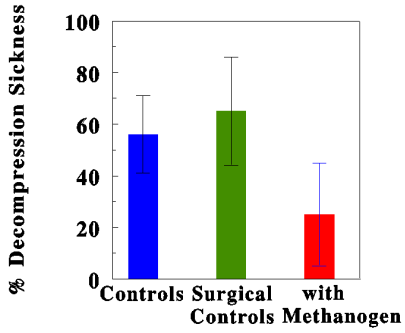

Figure 2. Rats treated with methanogenic microbes in their intestines had a significantly lower incidence of decompression sickness than untreated control animals or surgical control animals, following a chosen compression and decompression sequence in hyperbaric hydrogen. (Error bars are 95% binomial confidence limits.)

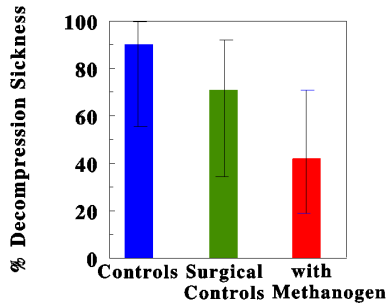

Figure 3. Pigs treated with methanogenic microbes in their intestines had a significantly lower incidence of decompression sickness compared to untreated and surgical control animals, following a chosen compression and decompression sequence in hyperbaric hydrogen. (Error bars are 95% binomial confidence limits.)

Based on these results with animals, the course of action to follow with human divers is clear. The microbes must be prepared for inserting into capsules to be taken by mouth. These capsules must be designed to withstand a 12-hour transit through the stomach and small intestine, since stomach acids and oxygen are fatal to the microbes. Much work remains to determine the optimal dose and timing of the microbial treatments, and of course safety issues must be continually addressed. However, the concept of hydrogen biochemical decompression is assured.

Given the limited application of hydrogen as a diving gas, it is far more intriguing to consider nitrogen biochemical decompression. There are nitrogen-metabolizing bacteria that are native to the intestinal flora of humans. The same general principles of the physiology of gas transport and the benefits of gas scrubbing on decompression sickness risk should apply to nitrogen as well as to hydrogen. However, the rate of nitrogen fixation is one to two orders of magnitude slower than for hydrogen metabolism. It would require a volume of bacteria too large to insert into the intestines of a person to remove a useful volume of nitrogen on a time scale of minutes to a few hours. Genetic engineering of nitrogen-fixing bacteria may some day advance to the stage at which we can actually envision a pill against decompression sickness for air divers.

Perfluorocarbons

We have also been developing at our institution an approach to reducing decompression sickness risk that is much easier to envision having an impact on diving safety very soon. Liquid perfluorocarbons are synthetic oils that can dissolve and transport large quantities of gases. Due to their high solubility for oxygen, perfluorocarbons are currently being tested in other laboratories as blood substitutes, and are also well-known as the substance to be used to fill the lungs in “liquid breathing”. Less-often considered is that perfluorocarbons have high solubilities for nitrogen and helium as well, which makes them potentially useful for treating diving casualties (Spiess et al., *Undersea Biomed. Res. 15*:31-37, 1988). Due to increased solubility of gases, intravenous injections of perfluorocarbons could improve inert gas elimination from tissues and decrease the number of circulating bubbles. These two actions should decrease the incidence or severity of decompression sickness for people at unusually high risk for decompression sickness, such as military divers on combat missions, or submariners in a rescue from a disabled submarine.

Research results so far with pigs are highly encouraging. Animals were exposed in a dry hyperbaric chamber to a compression and decompression sequence in air. Untreated animals had a 90% incidence of decompression sickness, whereas animals treated with perfluorocarbons had only a 53% incidence (Figure 4). This treatment was given to animals within a few minutes after decompressing, with initial symptoms of decompression sickness typically manifesting themselves within 5 to 20 minutes of decompression. The possibility exists that decompression sickness risk could be lowered further with more testing of doses or timing of perfluorocarbon delivery.

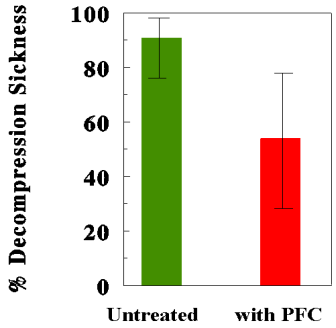

Figure 4. Pigs treated with intravascular injections of perfluorocarbons have a significantly lower incidence of decompression sickness than untreated pigs, following a chosen compression and decompression sequence in air. (Error bars are 95% binomial confidence limits.)

Immune System Interactions

Research from our laboratory and that of a number of others in recent years has indicated that much of what we associate with symptoms of decompression sickness may be an inflammatory response to bubbles or to tissue damage, rather than a direct embolizing effect of the bubbles themselves (Ward et al., *Undersea Biomed. Res. 17*:51-66, 1990). If the immune system plays a significant role in the manifestations of decompression sickness, then it may be possible to prevent or treat decompression sickness through manipulation of the immune system. Researchers at our institution are analyzing the plasma of animals with decompression sickness for such inflammatory marker molecules as interleukins, tumor necrosis factor, complement, and intercellular adhesion molecules. Results of these experiments are not yet available. However, this direction may well prove to be the most fruitful of all in identifying a safe and effective means of decreasing decompression sickness risk for all divers.

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